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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/921,937	08/03/2001	Marc Feldmann	65019-DC-PCT-US/JPW/AJM/N	1212

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EXAMINER	
GAMBEL, PHILLIP	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/921,937	FELDMANN ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55,60 and 70-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55,60 and 70-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 7/29/04, has been entered.
Claims 1-54, 56-59, 61-69 have been canceled.
Claims 55 and 60 have been amended.
Claims 70-87 have been added.

Claims 55, 60 and 70-87 are pending.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Action will be in response to applicant's arguments, filed 7/29/04.
The rejections of record can be found in previous Office Action.

3. The filing date of the instant claims is deemed to be the filing date of parent application USSN 08/690,775, i.e. 8/1/96. Priority application USSN 08/403785 and PCT/GB94/00462 does not support the broader claims of the instant application, including "preventing arthritis with anti-TNF antibodies and methoxtrexate", the specific administration protocols recited in instant claim 55(a)(b), a dose of "7.5 mg/wk or more" (e.g. claim 70 and 75), "1 mg/kg or more" (e.g. see claims 71-72, 80-81) as well as the specific limitations concerning the specificity of the claimed antibodies recited in the instant methods (e.g. see claims 74-78, 83-84 and 87).

If applicant desires priority prior to 8/1/96; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Applicant's assertions of priority back to USSN 07/958,248, filed 10/8/92, including direction to certain passages of the USSN 07/958,248 disclosure, have been fully considered but are not found convincing.

For example, there does not appear to be sufficient written description for "preventing arthritis", the specific administration protocols recited in instant claim 55(a)(b), a dose of "7.5 mg/wk or more" (e.g. claim 70 and 75), "1 mg/kg or more" (e.g. see claims 71-72, 80-81) as well as the specific limitations concerning the specificity of the claimed antibodies recited in the instant methods (e.g. see claims 74-78, 83-84 and 87)..

Applicant's reliance on USSN 08/403,785, now U.S. Patent No. 5,741,488 ('488 Patent) and PCT International Application No. PCT /GB94/00462 and the incorporation by reference to USSN 07/943,852 is acknowledged.

USSN 07/943,852 was not available to the examiner at this time. Therefore a complete analysis concerning applicant's reliance upon 08/403,785 and, in turn on USSN 07/943,852 for priority has not been done.

The examiner apologizes for any inconvenience to applicant in this matter.

At most, applicant's reliance upon incorporation by reference to USSN 07/943,852 may provide written support for the specific limitations concerning the specificity of the claimed antibodies recited in the instant methods (e.g. see claims 74-78, 83-84 and 87).

However, there still appears to be a lack of written support, hence priority, for "preventing arthritis with anti-TNF antibodies and methotrexate", the specific administration protocols recited in instant claim 55(a)(b), a dose of "7.5 mg/wk or more" (e.g. claims 70, 72, 75, 79), "1 mg/kg or more" (e.g. see claims 71-72, 80-81), as indicated herein.

A claim as a whole has only one effective filing date.
See e.g. Studiengelsellschaft Kahle m.b.H. v. Shell Oil Co. 42 USPQ2d 1674, 1677 (Fed. Cir 1997)

It is noted that entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed. See Lockwood v. American Airlines Inc., 41 USPQ2d 1961 (Fed. Cir. 1977).

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 70-72, 79-81 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed.

The specification as originally filed does not provide support for the invention as now claimed:

"the specific administration protocols recited in instant claim 55(a)(b), a dose of "7.5 mg/wk or more" (e.g. claims 70, 72, 75, 79), "1 mg/kg or more" (e.g. see claims 71-72, 80-81), as indicated herein.

Although applicant's amendment, filed 7/29/04, directs support to certain pages of the instant specification for the written description for the above-mentioned "limitations"
there does not appear to be sufficient written description for the specific "limitations" above.

The specification as filed does not provide sufficient written description for these "limitations". The specification does not provide sufficient blazemarks nor direction for the instant methods encompassing the above-mentioned "limitations" as currently recited. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Such limitations recited in the present claims, which did not appear in the specification, as filed, introduce new concepts and violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office Action

Alternatively, applicant is invited to provide sufficient written support for the "limitations" indicated above. See MPEP 714.02 and 2163.06

6. The previous rejection under 35 U.S.C. § 112, second paragraph, with respect to the recitation of "tumor necrosis factor-mediated disease" has been obviated by the absence of this limitation in the current claims.

7. The previous rejection under 35 U.S.C. § 102(e) as being anticipated by Mak et al. (U.S. Patent No. 6,190,691) has been obviated by the applicant's amended and canceled claims.

8. Claims 55, 60 and 70-87are rejected under 35 U.S.C. § 103 as being unpatentable over Mak et al. (U.S. Patent No. 6,190,691) AND/OR Adair et al. (U.S. Patent No. 5,994,510) (1449) in view of the Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1305-1312) and Aggarwal et al. (U.S. Patent No. 5,672,347) (1449) essentially for the reasons of record.

Applicant's arguments in conjunction with Exhibits, filed 7/9/04, have been fully considered but are not found convincing essentially for the reasons of record.

It is noted that the instant application as filed appears to support assertions of unexpected results as they would read on "methotrexate being administered in the form of a series of low doses separated by intervals of days and weeks (e.g. see Summary of the Invention, particularly, page 4, lines 23-25) and that therapeutically effective amounts are not necessarily an amount such that administration of the TNF antagonist alone or the administration of methotrexate alone would necessarily results in inhibition of the biological activity of TNF (e.g. see page 37, line 26-30 of the instant specification).

The instant claims do not recite such limitations of "low doses of methotrexate" nor "therapeutically effective amounts of either anti-TNF antibodies or methotrexate, wherein each alone does not necessarily result in the inhibition of biological activity of TNF".

For example, applicant relies upon the administration of 7.5 mg/wk of methotrexate, yet this appears to be a standard dose of methotrexate for arthritis patients (e.g. see Example 1 on page 40 of the specification).

Applicant's reliance upon Verhoeven et al., British Journal of Rhematology 37: 612-619, 1998 and Genovese et al., Arthritis and Rheumatism 50: 1412-1419, 2004 is acknowledged. Here, applicant underscores their position that many combinations of drugs do not improve treatment of human patients with active rheumatoid arthritis and the superior effects of a particular combination therapy in the treatment of inflammatory disease are not predictable absent experimentation.

It appears that neither Verhoeven et al. or Genovese et al. describe the unexpected results of combining anti-TNF antibody with methotrexate. Verhoeven et al. describe combinations of non-antibody antagonists of disease modifying anti-rheumatic drug therapy and Genovese et al. describes combinations of anti-cytokine antibody antagonists. It is noted that the patients described by Genovese et al. are receiving stable doses of methotrexate and other medications (e.g. corticosteroids) throughout the study (see Study Design and Treatment on page 1413, column 1). Therefore, it appears that Genovese et al. supports the baseline treatment of arthritis patients with methotrexate coupled with other known anti-inflammatories such as corticosteroids along with an additional arthritic antagonists such as TNF

antagonists, including anti-TNF antibodies. The lack of benefit of combination therapy based upon anti-IL-1 antibody therapy and anti-TNF antibody therapy may have been attributed to the degree of overlap and interplay between IL-1 and TNF (see page 1418, column 1, paragraph 1 of Genovese et al.). Thers is insufficient objective evidence to suggest that there would have an expectation of negative interactions of administering known methotrexate therapy for arthritis patients along with the prior art teaching of anti-TNF antibody to treat the same patients.

Applicant is invited to consider addressing the issues of dosing such that therapeutically effective amounts which are not necessarily an amount such that administration of the TNF antagonist alone or the administration of methotrexate alone would result in inhibition of the biological activity of TNF (e.g. see page 37, line 26-30 of the instant specification).

The record, particularly Genovese et al. appears to be consistent with the prior art rejection of record that the ordinary artisan would have had an expectation of success in combining the standard or common practice of treating arthritis patients with methotrexate (and corticosteroids) coupled with an antagonist such as anti-TNF antibody, which acts via a different mode of action from such DMARDs and specifically targets an important inflammatory cytokine associated with the arthritis.

Mak et al. teach the use of TNF antagonists, including anti-TNF antibodies (e.g. column 7, paragraph 3; column 9, paragraph 3; column 11, paragraph 3; column 42, paragraph 3) in combination with methotrexate (column 41, paragraph 2; Immunosuppressants; columns 59-61, including column 60, paragraph 1) in various dosages and schedules (columns 53-56) to treat rheumatoid arthritis (e.g., see column 2, paragraph 1; column 3, lines 48-55; column 8, paragraphs 1 and 3; column 9, paragraphs 2-3; column 64, paragraph 1-2) (see entire document, Summary of the Invention, Detailed Description of the Invention, including columns). Mak et al. differs from the claimed invention by not disclosing the well known use of recombinant antibodies.

Adair et al. teach the use of recombinant anti-TNF antibodies and fragments thereof to treat autoimmune diseases, including arthritis (see column 11, paragraph 8), alone or in combination with other active ingredients (column 11, paragraph 5), including well known methods of modes of administration (column 12)(see entire document). Adair et al. differs from the claimed methods by not disclosing the well known use of methotrexate in the treatment of arthritis

Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992) disclose the well known use of methotrexate in the treatment of rheumatoid arthritis; pages 1305-1312, particularly page 1311, Cytotoxic or Immunosuppressive Drugs).

Given the teachings of Mak et al., Adair et al. and the Merck Manual of Diagnosis and Therapy, one of ordinary skill in the art at the time the invention was made would have been motivated to select the combination of anti-TNF antibodies in combination with the immunosuppressant methotrexate to treat rheumatoid arthritis. Given the inhibitory properties of the referenced anti-TNF antibodies by Mak et al. and Adair et al., the claimed functional and epitope specificities, including the cA2 competing antibodies would have been expected or intrinsic properties of the referenced anti-TNF antibodies. Providing the claimed recombinant anti-TNF antibodies and fragments thereof encompassed by the instant claims (e.g. chimeric,

humanized, resurfaced antibody) would have been obvious to the ordinary artisan to provide therapeutic antibodies in order to decrease the immunogenicity of therapeutic antibodies and to increase half-life of antibodies to achieve effective amounts of anti-TNF antibodies. The various therapeutic modalities are either explicitly taught by Mak et al. or would have been obvious to one of ordinary skill in the art to provide effective therapeutic amounts of immunosuppressive regimens in order to meet the needs of the patients, herein, patients with rheumatoid arthritis.

In addition to teaching the use of anti-TNF antibodies to treat various autoimmune diseases, Aggarwal et al. teach that the combination of TNF antagonists and anti-inflammatory agents provides for the use of these agents in lesser dosages when used alone. An ordinary artisan would have been motivated to provide anti-TNF antibodies to lessen the amount of methotrexate, given its know toxicities at the time the invention was made. It was prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See MPEP 2144.06. Here, the prior art teaches combining antagonists encompassed by the claimed invention by teaching the use of anti-TNF antibodies and/or methotrexate to treat rheumatoid arthritis with other agents to inhibit the same disease. Here, too, the references teach the art known advantages of employing two immunosuppressives at the time same time, as evidenced by Aggarwal. et al.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention

13. Claims 45-46 are rejected under 35 U.S.C. § 103 as being unpatentable over Mak et al. (U.S. Patent No. 6,190,691)(1449) AND/OR Adair et al. (U.S. Patent No. 5,994,510) (1449) in view of the Merck Manual of Diagnosis and Therapy (Sixteenth Edition, 1992; pages 1338 and 2435-2437)and Aggarwal et al. (U.S. patent No. 5,672,347) (1449),
as applied to claims 32-37, 42-50 and 55-63 above and further in view of Le et al. (U.S. Patent No. 5,919,452) (1449).

The above teachings did not disclose the particular anti-TNF cA2 specificity encompassed by claims.

Le et al. teach the use of chimeric anti-TNF antibodies, including the cA2 specificity (columns 10-20) to treat a number of TNF related pathologies (columns 33-35; Therapeutic Methods of Treating TNF-Related Pathologies), including known methods of administration to achieved the desired effect alone or in combination with other therapeutic agents (columns 35-38, Therapeutic Administration) (see entire document, including Detailed Description of the Invention and Claims)

Given the properties of the anti-TNF, particularly cA2-specific antibodies taught by Le et al., one of ordinary skill in the art would have been motivated to substitute or to apply this inhibitory cA2 anti-TNF antibody to treat rheumatoid arthritis as taught above. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in

producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention

15. Claims 32-37, 42-50 and 55-69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,270,766. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims anticipate the instant claimed methods.

16. Claims 32-37, 42-50 and 55-69 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,270,766. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims anticipate the instant claimed methods.

17. Claims 32-37, 42-50 and 55-69 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims of copending application USSN 09/754,004. Although the conflicting claims are not identical, they are not patentably distinct from each other because the pending claims of the instant and copending applications are drawn to the same or nearly the same methods of treating tumor necrosis mediated diseases by administering methotrexate and a TNFα antagonist, including TNFα-specific antibodies, as the elected invention in each application.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

18. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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